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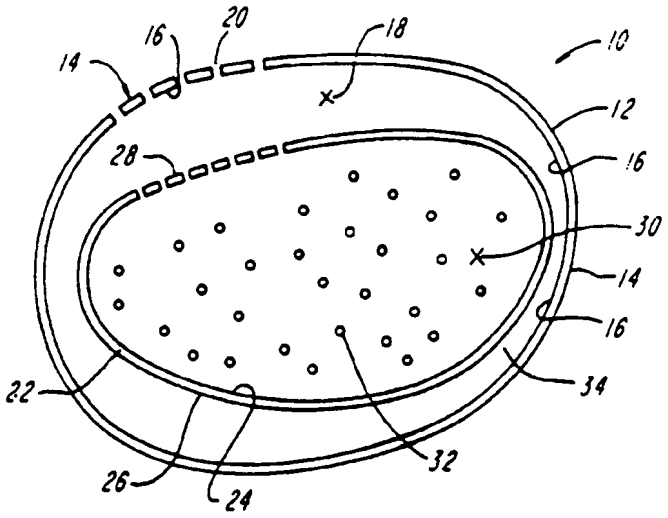

(57) Abstract

Implantable artificial organs are disclosed for delivery of a biological agent from implanted cells placed within the body cavity of a subject. The cells (32) are maintained within a selectively permeable membrane (22), which permits the movement of the agent therethrough while excluding white blood cells (immunocytes), antibodies and other detrimental agents present in the environment of use from gaining access to the cells. The selectively permeable membrane is completely enclosed by a perforated housing (12) which protects the membrane from breakage and permits body fluids to be in close contact with the membrane. Implantable artificial organs are disclosed, all of which may be retrieved from the subject, replaced or recharged and reimplanted.

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IMPLANTABLE ARTIFICIAL ORGAN

BACKGROUND OF THE INVENTION

Semipermeable membranes containing a cell which produces a biologically active substance often are implanted into a subject's body for a variety of purposes. The membrane allows bodily fluids to diffuse in and out of the membrane but prevents the movement of the subject's immune cells into the membrane. As a result, implantable semipermeable membranes have been used to immunoisolate parasitic cell or infective larvae in studies relating to the immune response of a host to parasitic infection. Diffusion housings have also been used to study in vivo or in vitro bacterial pathogenesis, e.g., Bordetella pertussis pathogenesis.

Much research has been focused on the use of semipermeable diffusion membranes for treatment of diabetes. Using such methods, pancreatic islet cells are enclosed in a semipermeable diffusion membrane which is then implanted in a diabetic mammal. Insulin diffuses through the diffusion membrane and can ameliorate diabetic conditions for limited periods of time. Nutrients diffuse through the membrane to support metabolism of islet cells.

Implantable, semipermeable diffusion membranes have a number of disadvantages. Most significantly,

implantation of numerous semipermeable membranes such as beads, straws, or discs into a body cavity of a patient in large numbers makes retrieval extremely difficult, if not impossible. In the case of cells with a limited life span, re-implantation of the individual membranes containing fresh cells is very difficult, time-consuming and dangerous to the patient, especially if the membranes become scattered throughout the body cavity by movement of the patient. Furthermore, diffusion membranes are subject to breakage during, and after, the implantation process and during subsequent activity of the patient. Breakage of the membranes can lead to spillage of the enclosed cells, thus exposing the cells to the patient's immune system. Rejection of the cells and non-specific inflammatory reactions often result, and this can cause significant morbidity in patients, particularly if such membranes are placed in the peritoneal cavity. Also, use of an agent, such as epoxy to seal the ends, sides, or circumference of the semipermeable diffusion membranes is problematic since the epoxy may volatilize within the body and release unwanted organic chemicals that are possibly toxic to the implanted cells.

It is appreciated by those of ordinary skill in the art that several hundred diffusion membranes are often needed to ameliorate diabetic conditions in dogs. Thus, implantation of several hundred individual membranes in a human poses almost insuperable problems with regard to breakage of the membranes and retrieval of the membranes.

SUMMARY OF THE INVENTION

The present invention pertains to an artificial implantable organ. The artificial organ includes a first housing having at least one interior and at least one exterior surface. The interior surface(s) define a chamber and the exterior and interior surfaces are in fluid communication with each other. At least a portion of the first housing is accessible to bodily fluids. A membrane is disposed within the chamber, at least a portion of the membrane being selectively permeable to bodily fluids. The membrane contains one or more cells ("cells") capable of producing a biological agent such as a hormone, cellular growth factor, and the like. The cells are preferably disposed entirely within the confines of the membrane. Preferably, the first housing is a geometrical shape having interconnected interior surfaces and exterior surfaces. The interior and exterior surfaces in closest facing relationship to each other are perforated. In this way, the housing can be arranged to allow bodily fluids to pass transversely through the housing to completely and persistently be in contact with the semipermeable membrane. The selectively permeable membrane allows nutrients in body fluids to pass through it to nourish the contained cells and permits a biological agent produced by the cells to pass through the membrane. The membrane prevents the cells from immunological attack, rejection, or physical escape.

The selectively permeable membrane that is

disposed within the chamber of the first housing can include a plurality of tubular membranes. In one embodiment of the invention, these tubular membranes are arranged within the chamber in a pinwheel configuration. In another embodiment, a plurality of tubular membranes are arranged parallel to each other within the chamber. Further configurations of the invention include a single, tubular membrane coiled within the chamber. The tubular membrane can also be coiled around a second housing that is concentrically disposed within the chamber of the first housing. Further embodiments include a cellular growth factor disposed within the membrane.

A preferred selectively permeable membrane is a tube with closed ends whose total length is substantially greater than any linear dimension of the first housing. In another preferred embodiment, the selectively permeable membrane is a closed tube disposed within the chamber of the first housing, the tube having an internal volume that is substantially equal to the internal volume of the chamber.

The implantable artificial organ is assembled and loaded with cells prior to implantation. Kits of the invention therefore include loaded and assembled artificial organs.

The invention also pertains to methods for delivering a beneficial agent to a body using the artificial organ of the invention.

It is also an object of the present invention to provide an artificial implantable organ that is easily retrievable.

It is a further object of the present invention to

provide an artificial implantable organ that protects a selectively permeable membrane from breakage during the implantation process.

It is yet another object of the present invention to provide an artificial implantation organ that is easily fabricated from readily available materials.

It is another object of the present invention to provide an artificial organ containing a selectively permeable membrane, which membrane is designed to minimize its sealed edges, while maximizing the total surface area thereof.

It is a further object of the present invention to provide an artificial organ utilizing selectively permeable membranes, which organ is small enough to be implanted into the abdominal cavity with minor surgery under local anesthetic or laparascopic techniques.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic, cross-section illustration of the implantable artificial organ of the present invention;

Fig. 2 is a schematic, top-view illustration of another embodiment of the implantable artificial organ of the invention;

Fig. 3 is a cross-sectional view through line A-A of the embodiment of Fig. 2.

Fig. 4 is a schematic, top view illustration of another embodiment of the implantable artificial organ of the invention;

Fig. 5 is a cross-sectional view through line B-B of the embodiment of Fig. 4.

Fig. 6 is an alternate embodiment of Figs. 4 and 5 5 in cross-sectien.

Fig. 7 is a schematic, top view illustration of another embodiment of the implantable artificial organ of the invention;

Fig. 8 is a partial cut-away view of another embodiment of the implantable artificial organ of the invention.

Fig. 9 is a partial cross-sectional view through line C-C of Fig. 8.

Fig. 10 is a partial cross-sectional view of an alternate embodiment of Figs. 8 and 9.

Fig. 11 is a schematic, cross-sectional illustration of another embodiment of the implantable artificial organ of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to an artificial organ for implantation into a subject, and processes for implanting and using such organs within the body of the subject. The term "subject" in this context refers primarily to humans, although non-human vertebrates such as primates, dogs, cats, horses and the like are also included within the meaning of the term.

Various characteristics of the implantable artificial organ are controlled so that the organ has the capability of preventing entry of immunologically active substances (i.e. lymphocytes, macrophages, circulating antibodies, and the like) into the artificial organ, thus simultaneously housing

biologically active cells in the organ and protecting the cells from the immunologically active substances. At the same time, the artificial organ permits the ingress of nutrients and body fluids therein and permits the egress of waste products and biological agents produced by the biologically active cell from the artificial organ. The result is a viable, ongoing source of a biological agent contained within the artificial organ which functions on a relatively long-term basis without rejection (immunological destruction) by the subject.

Fig. 1 illustrates in schematic form a cross-sectional view of the general construction and operation of the present implantable artificial organ. The artificial organ 10 includes a first, three-dimensional housing 12 having at least one exterior surface 14 and at least one interior surface 16. In Fig. 1, the first housing 12 is a hollow sphere with one interior and exterior surface. The interior surface 16 of the first housing 12 defines a chamber 18. At least a portion of the first housing's exterior 14 and interior 16 surfaces contain perforations 20 that render at least that portion of the first housing accessible to bodily fluids. A membrane 22 is disposed within chamber 18. Membrane 22 includes interior 24 and exterior 26 surfaces. A portion 28 of these surfaces 24,26 is selectively permeable to bodily fluids. The interior surface 24 of membrane 22 defines an internal volume 30, hereinafter referred to as a lumen. One or more biologically active cells 32 (hereinafter "cells") capable of producing a biological agent are disposed

completely within lumen 30 of membrane 22. The interior surface 16 of first housing 12 and exterior surface 26 of membrane 22 define between them a volume 34 that is accessible to bodily fluids. In Fig. 1., volume 34 is also free of the biologically active cells 32.

First housing 12 can be compatible with implantation into a living body and can be of sufficient thickness and of sufficient inflexibility to protect membrane 22 from breakage. The first housing 12 can be comprised of, for example, stainless steel, titanium, or other implantable substances, including organic polymers such as a variety of plastics, so long as the material is non-reactive (i.e. biologically inert). For example, the first housing can be polytetrafluoroethylene, silicon-coated plastic, polycarbonate, polysulfone, polymethyl methacrylate or mixtures thereof. The first housing can also be fabricated of woven or fibrous materials, such as, for example Dacron or polytetrafluoroethylene mesh.

As mentioned above, at least part of the first housing 12 is accessible to bodily fluids. The term "accessible" refers to a characteristic of at least part of the first housing 12 that allows bodily fluids to be in fluid communication with the housing without any restrictions or molecular size exclusions. The term "accessible" particularly refers to fluid communication that relies on passive movement of bodily fluids and is not meant to include fluid communication based upon connection of the artificial organ to blood vessels and/or lymph ducts for active

pumping of fluids through the artificial organ. "Bodily fluids" means plasma, blood, lymph, urine, salts, gases, metabolic products, solutes, cell cytoplasm, and other liquid and gaseous materials found within the body of a subject.

Accessibility to bodily fluids of the first housing 12 is effected by the presence of a plurality of perforations 20 that will allow the passive entrance and exit of bodily fluids. The perforations can include a variety of shapes and configurations. The perforations can be of any size, so long as the membrane 22 is protected from physical damage by adjacent body organs or cells.

In one embodiment (illustrated in Fig. 1), the first housing 12 has a plurality of perforations 20 of substantially circular cross section, each perforation consisting essentially of a thin tube extending from exterior surface 14 to the interior surface 16 of the first housing 12. In other embodiments, the perforations may include an interconnected matrix of substantially tubular pores. For example, if the first housing 12 is made of a woven material such as Dacron, or other similar polymer, the perforations 20 of first housing 12 are configured in a grid or mesh work configuration and include a lattice of overlapping and/or interconnected mesh.

Referring again to Fig. 1, the housing 12 completely encloses membrane 22. A "membrane" is a thin sheet or layer. At least a part of the membrane is selectively permeable. The term "selectively permeable" refers to membranes characterized in their ability to permit entry only of a certain kind and

size of material. A selectively permeable membrane 22 should bar components of the cell-mediated and humoral immunological responses, i.e., macrophages, complement, lymphocytes and antibodies from entry into the membrane while allowing the passage of bodily fluids (i.e. salts, blood plasma, blood, lymph, growth factors, nutrients, gases, metabolic breakdown products, solutes) and the biological agent produced by the cells to pass therethrough. Thus, in this manner, bodily fluids can pass into the membrane 22 and interact with the cells contained within the membrane. Any biological agent(s) released by the cells will exit membrane 22, pass through chamber 18, out of the housing 12 and be released into the body. Thus, the properties of the selectively permeable membrane allow it to act as a physical barrier to retain the cells within it while allowing non-cellular materials and products to pass unhindered, and to prevent antibodies and immune cells of a host from penetrating into the lumen of the membrane and destroying the cells. So long as these requirements are met and satisfied, neither the chemical composition of the selectively permeable membrane, nor the perforation size of the membrane is of any consequence. Although Fig. 1 illustrates a three-dimensional membrane 22 completely enclosing cells 32, it will be understood that membrane 22 can also contain cells 32 that are embedded or otherwise impregnated into the membrane material itself. For example, cells 32 can be supported on the interior surface 24; and/or between interior and exterior 26 surfaces.

The permeability of the membrane is a function of the composition of the particular materials used. Generally, any biologically inert material (i.e. incapable of initiating a biological reaction, such as an immune response, in the recipient subject) having perforations (referred to in this context as "pores") enabling passage of molecules with a molecular weight of between about 50,000-80,000 Daltons is useful for the membranes of the present invention.

Well-described and commercially available selectively permeable membranes composed of various compositions are available for the membrane. These materials include selectively permeable membranes made of acrylic resins, cellulose acetate, cellulose-nitrate, nylon, polycarbonate and other mixed esters. Preferably, the membrane is a porous acrylic copolymer membrane of about 50,000-80,000 Dalton average porosity such as the type XM manufactured by the Amicon Division of W.R. Grace and Company. The pore sizes of the preferred membranes are selected to provide a barrier to protect the cells from a host immune reaction. Those of ordinary skill in the art will appreciate that the appropriate pore size can be determined using no more than routine methods. For example, the pore size can be selected on the basis that the membrane must exclude greater than 90 percent of an IgG solution.

Because of this membrane, cells from a variety of sources can be implanted in a recipient subject without necessarily requiring drug-induced immune suppression of the recipient subject.

The membrane can be made in a variety of preferred

shapes and forms, as illustrated in more detail below. Each of the variety of different shapes and orientations will be constructed with a lumen volume to meet the requirements of the intended application. With embodiments of the artificial organ intended for human use, the lumen 30 of the membrane 22 can preferably range from about 0.02 to about 100 cubic centimeters and the effective distance between cells inside the membrane and the exterior surface of the first housing is preferably no greater than about 3.0 centimeters.

Generally, the membrane will be in the shape of a hollow tube or bag whose ends are sealed together using adhesives, heat, ultrasound and the like. An important feature of the present invention is that the membrane is designed to minimize the area of its sealed edges relative to its total surface area. In this way, the amount of sealed surfaces in contact with the environment of use is minimized. This is particularly important if epoxy adhesives are used to close the ends of the membrane. The epoxy resins may volatilize and/or release undesirable compounds into the environment of use. Moreover, manipulation and fabrication of the present implantable organs is simplified if the membranes are made with as few sealed edges as possible. Preferred constructions of the membrane designed to minimize the sealed surface area will be presented in more detail below.

Referring again to Fig. 1, cells 32 are contained within lumen 30 of membrane 22. Cells that are thus encapsulated and implanted may be "allografts," or cells implanted one member of a species to another of

the same species as the subject in which they are to be implanted, or they may be "xenografts", or those from another of a different species. More particularly, they may be a component (i.e. a portion or constituent) of a body organ which normally secretes a particular biological agent in vivo. The cells are desirably used as single, dispersed cells or in cell aggregate form. The actual cell size and the quantity of cells in the device of the present invention will depend to a significant degree on a correlation of various factors such as the chemical composition of the housing, membrane configuration, the construction of the device, the cells of choice, the disease to be treated, ameliorated or controlled, the environment of use including nutrients available for generating or promoting formation of a biological agent, and other considerations.

The artificial organ will contain a quantity of cells at least sufficient to produce a biological agent that effects a desired result, and/or treats, ameliorates and/or controls a targeted disease. Illustrative examples of cells (and the biological agent(s) produced by them) include cells from the thyroid (thyroid hormone), parathyroid (parathormone), adrenal gland (adrenalin, gluco-corticoids, steroids), nerve cells (nerve growth factors), liver cells (enzymes or coagulation proteins). It will be appreciated that the term "cells" can also include whole cell aggregates and can also include microorganisms such as bacteria and protozoans, capable of producing one or more biological agents. Moreover, genetically engineered

cells and cells modified by conjugation, hybrid DNA or fusion can be used. See, for example, Kawakami et al., Diabetes 41:956-961 (1992); Docherty, K., "Prospects For Gene Therapy And Cellular Engineering In Diabetes," pp. 154-182 in Biotechnology of Insulin Therapy, (ed. J.C. Pickup), Blackwell, London (1991), incorporated herein by reference. Further, cell types which can grow in suspension culture, as well as anchorage-dependent cells can be used in this invention. Specific examples include fibroblasts, leukocytes, lymphoblastoids, pituitary cells, and the like. The term "cells", as defined for the purposes hereof, can include cell fragments, cell clumps and single cells. It will thus be appreciated that the biological agent can augment activity of an organ within the body of a subject, which organ has lost its ability, or has a diminished capacity, to produce a biological agent.

The process and apparatus of this invention is particularly suitable for using pancreatic endocrine cell from pancreatic islets or islet cells for implantation into the body and for release of insulin. The optimal pancreatic islet cells for this function are substantially fibroblast-free cell preparations derived from cultured fetal islet cells or intact, whole organ pancreas, which are subsequently cultured in vitro. For purposes of clarity of explanation and not by way of limitation, the invention will be described hereinafter in terms of pancreatic islet cells, it being understood the process and product is also suitable for implanting other types of cells, as described above. These other types can be considered alternates in the invention

description.

The concentration of islet cells within the membrane can be from about 10^2 to 10^8 cells/ml. The pancreatic islet cells suitable for incorporation into the membrane of this invention can be derived from pancreatic cell by numerous published procedures or they can be derived from cell, organ or cell cultures. The term "pancreatic islets" includes the constituent cell types within the islet of Langerhans including beta cells, the actual producers of insulin, intact islets, islet fragments, genetically engineered islet cells or combinations of the foregoing. A procedure for isolating islets from a donor pancreas is described in Example 1.

The islet materials can also contain other cell which enhance islet viability. The presence of endothelial cells or fibroblasts can create an environment more like that in which islet cells naturally occur. Other cell types which produce growth factors and/or soluble, cellular growth factors or basement membrane components can be cultured with the islets and included within the membrane to enhance growth and viability.

Figs. 2 and 3 illustrate one embodiment of the artificial organ of the present invention. Generally, the first housing 12 is a geometrical shape with a plurality of interconnected exterior 17 and interior 15 surfaces. In Fig. 2, the first housing 12 is a toroidal or donut configuration. It will be appreciated that a disc, square, cylinder or rectangular shape will also be suitable. The toroidal first housing 12, shown in cross-section in Fig. 3.,

has two interior 15 and exterior 17 surfaces in closest facing relationship to each other. These particular surfaces contain perforations 20 and are accessible to bodily fluids. Interior surfaces of the first housing 12 define chamber 18. Because housing 12 is designed so that the surfaces in closest facing relationship to each other are accessible to bodily fluids, the housing will allow bodily fluids to pass transversely through it. The term "transversely" refers to bidirectional flow (shown by the double-headed arrows in Fig. 3), parallel to an axis of the housing, the axis defined by the housing surfaces in closest facing relationship to each other. The "depth" of housing 12 is also defined by the distance between those surfaces of the housing in closest facing relationship to each other. Perforations 20 on first housing 12 thus allow bodily fluids to flow between the surfaces that are in closest facing relationship to each other (i.e. "transversely" through the housing). The perforations 20 of the first housing can be of any shape or dimension, provided that they are smaller than the width (W) of the enclosed membranes 22, to prevent the membrane from escaping out of the first housing.

A plurality of selectively permeable membranes 22 is completely enclosed within chamber 18 of first housing 12. In the embodiment illustrated in Figs. 2 and 3, the membranes 22 are a plurality of tubular, selectively permeable membranes with closed ends 38, the membranes 22 being arranged in a pinwheel configuration within chamber 18. Each membrane of the pinwheel contains cells 32 for producing a biological

agent. Specifically, each individual membrane 22 is spaced apart from an adjacent membrane by between 1-5mm and each individual membrane is arranged radially around a central, membrane-free region 40 of the first housing 12.

The length of the individual membranes can range from about 1.0 to about 5.0 cm. The width of each individual membrane 22 can range from about 0.05 cm to about 1.5 cm. Most preferably, the membranes are about 1.0-5.0 cm long by about 0.5 cm wide. The number of membranes will depend upon the size of the first housing 12 and the spacing between individual membranes. Significantly the number of membranes in this embodiment, as in the other embodiments, will also be determined by the patient requirement for the biological agent. In the case of diabetes, for example, the number of membranes can be easily altered to provide a calibrated amount (e.g. 15, 30, 40 Units) of insulin for delivery.

The individual membranes can be tethered to each other using a biocompatible suture material or attached to an interior surface 15 of the first housing 12. Nevertheless, it is preferred that the individual membranes 22 not be bound together or be affixed to the inside of the first housing. Rather, as illustrated in Figs. 2 and 3, small sections of inert material 42 (hereinafter called "spacers") are constructed to protrude from interior surface 15 of the first housing 12. Spacers 42 physically separate individual membranes 22 and facilitate circulation of bodily fluids between membranes. The projection of the spacers into the housing can vary so long as they

effectively separate the individual membranes. Furthermore, the depth of first housing 12 (i.e., the distance between those perforated sides in closest facing relationship to each other) is designed so that transverse movement of the membranes within chamber 18 is severely constrained. The depth of the housing is substantially equal to the width (W) of the membranes. Thus, with this size limitation, plus the spacers, the membranes 22 will stay in place without movement.

The size of a typical toroidal first housing 12 ranges from about 3.0 cm in diameter to about 10.0 cm in diameter with a depth of about 1.5 cm. Most preferably, the first housing shown in Figs. 2 and 3 ranges from about 3.0 to about 8.0 cm in diameter.

Figs. 4 and 5 illustrate yet another embodiment of the artificial organ. In this embodiment, the first housing 12 is substantially rectangular in shape. The interior 15 and exterior 17 surfaces in closest facing relationship to each other contain perforations 20. Interior surfaces 15 define chamber 18. A plurality of selectively permeable, substantially tubular membranes 22 are disposed within chamber 18 and are arranged in parallel. The membranes have closed ends 38. Membranes 22 can be arranged to have a length (L) equal to a linear dimension (i.e., width or length) of the first housing, depending upon which orientation the membranes are placed. Each of the individual membranes 22 contain cells 32 and each membrane is separated from adjacent membranes by spacers 42 projecting from an interior surface 15 of the first housing. Movement of the individual membranes 22

within chamber 18 is constrained by the dimensions of the chamber. That is, the width (W) of any membranes will be substantially identical to the depth of the first housing. A rectangular first housing 12 of about 8.0 cm x 4.5 cm wide x 0.5 cm in depth is suitable for implantation in, for example, the abdominal cavity. The membrane can be about 8.0 cm long x about 0.5 cm wide.

Figure 6 illustrates an alternate embodiment with two layers of membranes. Reference numbers are identical to Fig. 5, except where indicated. A first housing 12 has a depth of about 1.0 cm, so that a second layer of membranes 46 is superimposed on top of the first layer of membranes 22. Preferably, spacers 48 are provided to separate the superimposed layers of membranes 22 and 46. Spacers 48 preferably traverse the inside of the first housing 12 either along its length, its width, or along both (e.g. in a criss-cross configuration). By thus expanding the depth of the first housing 12 to accomodate a plurality of membrane layers, additional biological agent can be released from the artificial organ.

Fig. 7 illustrates another embodiment of the artificial organ, showing a significant feature of the present invention; namely that the membrane is constructed to minimize the numbers of its sealed ends and maximize its total surface area. As shown in Fig. 7, a substantially disc-like first housing 12 completely encloses a tubular, selectively permeable membrane 22 whose length is substantially greater than any linear dimension of the first housing. In the particular embodiment illustrated, the membrane 22 is

a single, coiled tube containing cells 32. It will be readily appreciated that the surfaces available for sealing the membrane are limited to the ends 38 of the coiled membrane 22. This is but one construction that will minimize the ratio: numbers of sealed ends/total surface area of the membrane.

An interior surface 15 of first housing 12 defines chamber 18. Interior surface 15 has a central projection 50. Emanating radially outwardly from the central projection are a series of spacers 42, also protruding from surface 15. These spacers 42 separate the coils of the tubular membrane 22 from each other as it is wound within chamber 18 of housing 12. The first housing has interior 15 and exterior 17 surfaces in closest facing relationship to each other that contain perforations 20.

A preferred first housing is a disk about 8.0 cm in diameter x 0.5 cm in depth. The width (W) of the preferred single, coiled membrane 22 can be substantially equal to the depth of the first housing. The membrane 22 can be of any length; long lengths are easily obtainable by winding the membrane around the central projection 50 in progressively larger coils. It will be understood that more than one coiled membrane can be accommodated within the first housing as two or more layers. The number of such membranes (layers) will depend primarily upon the width of the membranes(s) and the depth of the first housing.

In another embodiment, the artificial organ includes a pair of concentrically arranged housings that are accessible to bodily fluids. The housings can be of any shape (i.e. square, circular,

rectangular, and the like). Most preferably, the concentrically arranged housings are cylindrical. In the embodiment illustrated in Fig. 8, an outer, first housing 100 is a cylinder with a diameter of between about 3 and 4 centimeters and a height of between about 6 to 10 centimeters. A second, inner cylindrical housing 105 is disposed in chamber 106, the chamber 106 defined by the interior surfaces 110 of the first cylindrical housing 100. The first cylindrical housing 100 has exterior surfaces 115. The second cylindrical housing 105 also has interior 120 and exterior 125 surfaces. A substantially annular volume 130 is defined between the interior surface 110 of first housing 100 and exterior surface 125 of second housing 105. Disposed within volume 130 is a selectively permeable membrane 135.

Most preferably, the selectively permeable membrane 135 is wound around the exterior surface 125 of the second, inner housing 105 as a plurality of coils, the coils separated from each other by a spacer (also in the shape of a coil) 150 that is supported on the exterior surface 125 of the second, inner housing 105. Cells 155 capable of releasing a biological agent, are disposed within the selectively permeable membrane 135.

The exterior and interior surfaces of both the cylinders preferably include perforations 160. The ends 165 of the first, outer housing 100 and the ends 170 of the second, inner housing 105, also include perforations 160 (end perforations are shown only for the interior housing in Fig. 8). The perforations 160 of the two cylindrical housings 100, 105 allow bodily

fluids to pass transversely across the device, as shown by the double-headed arrows in Fig. 9. Moreover, the perforated ends 165, 170 of the two cylindrical housings will allow bodily fluids to pass through the housings in a direction substantially orthogonal to the transverse flow (i.e., parallel to the longitudinal axis of the concentrically arranged housings).

Fig. 9 illustrates a partial cross-section through line C-C of Fig. 8, with identical reference numbers being used, except where indicated. It can be appreciated that the total length of membrane 135 is the sum of number of coils x the length of each coil, where the length of each coil is
diameter of the inner housing 105. The width (W) of the annular volume 130 (i.e. the distance between the respective surfaces 110, 125 of the two cylindrical housings) is preferably substantially equal to the diameter of the selectively permeable membrane 135. This will insure that the selectively permeable membrane is constrained within the annular volume, in a manner analogous to the constraints imposed by the dimensions described in the previous embodiments of this invention.

In the embodiment illustrated in Figs. 8 and 9, the second, inner housing is not fixed to the first, outer housing. That is, neither exterior surface 125, nor ends 170 of the second, inner housing 105 are attached to the outer housing 100. It will, however, be understood that one, or both, ends 170 of the second, inner housing 105 can be affixed to the respective ends 165 of the first, outer housing 100

without departing from the scope of the invention.

For example Fig. 10 illustrates an alternate embodiment of Figs. 8 and 9 in which inner housing 105 is integral with an end 165 of outer housing 100. Inner housing 105 lacks a separate perforated end section so that interior 120 and exterior 125 surfaces of inner housing 105 abut directly against end 165 of the outer housing 100. All reference numbers are identical to those in Figs. 8 and 9.

Fig. 11 illustrates yet another embodiment of the invention. A substantially disc-shaped first housing 12 is shown, with interior and exterior surfaces 15, 17, respectively, in closest facing relationship to each other containing perforations 20 and being accessible to bodily fluids. A tubular, selectively permeable membrane 22 containing cells 32 is disposed completely within chamber 18, the chamber defined by interior surfaces 15. As shown in cross-section, the membrane 22 defines a lumen 30 that takes up almost the entire chamber volume. The lumen 30 of membrane 22 can have a volume from about 1% to about 5% smaller than the volume of chamber 18. The sealed edges 38 of membrane 22 are shown in the cross-sectional view. It will be appreciated that the ratio of the sealed surface area of the member to the total surface area of the membrane is also at a minimum in this particular configuration.

Additional embodiments of the present invention can be readily appreciated by those of ordinary skill in the art. For example, the artificial organ of the present invention can include one or more first housings stacked together as a unit, each of the first

housings containing a membrane enclosing cells, as described herein. Moreover, the membrane can be impregnated or filled with a cellular growth factor or other material to enhance growth of the enclosed surrounding cells. Growth factors or other agents such as angiogenic factors, interleukins, chemotactic factors, and the like are well known to those of ordinary skill in the art.

Alternately, or in addition, a matrix of collagen or other structural material can be incorporated within the membranes. This matrix would allow growth of capillaries which may provide additional nourishment for the cells within the membranes.

The artificial organs of the present invention can be easily fabricated using conventional methods.

Metallic housings can be fabricated using conventional milling procedures. If plastic, housings can be made using conventional lamination, extrusion and/or molding procedures. Perforations can be drilled or incorporated in a mold. Generally, the first housings are fabricated as open discs or boxes with no top. The depth of the box plus the top is about equal to, or only slightly larger than, the width of the membrane that is to be placed in the first housing. The membranes are loaded with cell, sealed, and then placed within the first housing. The presence of spacers on the interior surfaces of the first housing aids in the correct positioning of the membrane(s).

With particular regard to Fig. 2, the toroid is fabricated with a central core, sidewalls, and no top. The depth of the completely assembled toroid,

including top, is approximately 1-5 mm larger than the width of the membranes. The interior surface of the toroid has spacers protruding from it and the membranes are placed in between the spacers. Each membrane has two sealed ends abutting the outer periphery of the toroid at their one end, and the interior central core of the toroid at their other end. Once the device is loaded, a top is then provided and secured by epoxy or screws.

With regard to Fig. 3, the first housing is constructed essentially like a cigar box without a top and with a depth slightly greater than the width of the individual membranes. The membrane is of length equal to a linear dimension of the first housing (i.e., width or length) depending upon the way the membranes are placed. The interior surface of the first housing includes spacers to separate the membranes from each other. The first housing is closed by attaching a lid with epoxy or screws, as with the previous embodiment. The space between the membranes is formed by the spacers in order to provide free flow of bodily fluid around the membrane.

With regard to Fig. 7, the configuration embodied therein is substantially a circular pill box with no top and a central post positioned on a interior surface of the pill box. Emanating from the central post are spacers which separate the coils of the membrane at equal intervals as the membrane is wound around the central post. The membrane is filled with the appropriate pancreatic islets and the ends of the membrane are sealed. The membrane is then be wound around the central post in between the spacers. A top

of the first housing is placed on the pill box with epoxy or screws, as described above. Alternatively, the membrane can be sealed at one end, wound around the central post, and then filled and sealed while it is in the open pill box. Then, the top is placed on the open pill box.

The concentrically arranged cylinders of Figures 8-10 is assembled in a similar manner. The membrane is filled with the appropriate pancreatic islets and the ends of the membrane are sealed. The membrane is then be wound around the inner housing in between the spacers. An open end of the first, outer housing is sealed by placing a perforated end section on the outer housing with epoxy or screws, as described above. Alternatively, the membrane can be sealed at one end, wound around the inner housing, and then filled and sealed while it is in the open outer housing. Then, the end is placed on the outer housing.

The invention also pertains to artificial organ kits used for ease of surgical operations. The kit contains a membrane filled with a biologically active cell (i.e. pancreatic islet cells). The membrane is contained within the first housing, as described herein and completely assembled, either in the operating room immediately pre-operation, or assembled in a laboratory and shipped to the operating room in a sterile container. Sterilization using, for example, ethylene oxide, and methods of shipping and packing medical devices to maintain sterility are well-known to those workers of ordinary skill in the art.

The implantable artificial organ of the present invention can be placed in any body cavity. The

preferred location within a preferred subject (i.e. a mammal such as a human) is the peritoneal cavity. The most preferred location in human subjects is in the lower abdominal cavity; in the area called the "anatomic pouch of Douglas". The pouch of Douglas is the deepest, most dependent portion of the peritoneal cavity in a patient that is standing erect. The artificial organ of the invention is placed in the "pouch of Douglas" and allowed to be passoively bathed with bodily fluid in the abdominal cavity. About 500 cc's of saline solution is added to the pouch area so that the artificial organ housing is well bathed initially.

The artificial organ is placed in a body cavity of a subject by a lower abdominal mid-line incision performed under local anesthesia. This involves, at best, day surgery, i.e. the patient comes in the morning, has the placement done, and is allowed to go home on the same day. The length of the lower abdominal mid-line incision is determined by the maximum diameter or length of the first housing. A first housing can be made small enough so that it could be inserted by laparoscopic techniques. This can be done if the first housing is constructed as a rectangle with a measurement of perhaps 2 or 3 cm by 6 or 8 cm. Once implanted, the functioning of the implantable artificial organ can be easily tested by monitoring bodily fluids of the subject for the particular beneficial agent expected to be produced by the cell. Increases in levels over "background" (i.e. preimplantation) indicate the implantable organ is functioning.

Without question, the placement of the artificial organ of the invention in the human body must have the possibility of being completely removed, retrieved, and/or recharged and reimplanted utilizing relatively simple methods. If one were to have membranes by themselves in the abdominal cavity in multiple numbers, i.e. 50, 100 or 200 membranes, the chances of retrieving them completely and easily would be extremely difficult. Membranes, enclosed within, and protected by, a first housing makes retrievability of the artificial organ very easy. The housings would be removed and possibly re-implanted with fresh cells the same way they were placed, i.e. through a lower mid-line abdominal incision performed under local anesthesia. Placement or removal of the artificial organ in the pouch of Douglas can be a simple operation of very short duration.

The artificial organs are ideal for placement in the abdominal pouch of Douglas in that their configuration and their weight maintain the artificial organ housing in the pouch area. The artificial organ can also be anchored in the pouch of Douglas by a single suture or two to the posterior parietal peritoneum. Thus, ease of placement, security of placement, and anchoring of placement in this area are advantages inherent in the present invention. Since the artificial organ is preferably located in that portion the of the body where peritoneal fluid collect, because of dependency (i.e. being the lowest portion), the device is continually bathed in bodily fluids.

The artificial organ of the invention also

protects the membranes from being broken while in the body and therefore protects their integrity from a possible immune rejection from the body's immunological reactivity. Most prior art diffusion membrane configurations are such that the membrane is easily breakable because of torque or twisting imposed on the membranes when they move around freely in the abdominal cavity. Since the membranes of the present artificial organ are prevented from movement and protected from outside pressures, the likelihood of them breaking is essentially zero.

The use of certain configurations of the membranes permits reduction or minimization of the number of ends that have to be sealed to contain the cells. For instance, in the embodiment of Fig. 4, only two ends need to be sealed, irrespective of the length of the membrane. Thus, with a membrane length of 80 cm, only two ends would have to be sealed; if 40 membranes of 2 cm each were used (80 cm total length), one would have to have 80 such seals. The advantage of just having two ends to seal is manifest.

The invention will now be further illustrated by the following non-limiting example.

EXAMPLE I

Isolation of islets from pancreatic tissue

Islets of Langerhans are obtained from the pancreas of donor animals (e.g. dog, cattle, pig). Islets of Langerhans are isolated and purified by modifications of published procedures. See, Gotoh et al., Transplantation, 40(4):437-438 (1985). Briefly,

an intact pancreas is infused by way of the pancreatic duct with a suspension of collagenase which digests connective tissue and disrupts the integrity of the gland. The gland is further dissociated by shaking it until cell fragments become small, centrifuging the fragments, and passing the pelleted fragments through a mesh filter (opening 860 microns, Bellco, Vineland, NJ) to remove the large undigested tissues, which usually consists of mesenteric lymph nodes and large vessel fragments. This dissociation procedure releases islets from the tissue that surrounds them. Islets are then separated from non-islet cell by centrifugation (800g for about 10 minutes) on a discontinuous gradient of Ficoll (Pharmacia Fine Chemicals, Inc.) (23% w/v; 20.5% w/v; and 11% w/v), which utilizes the difference in density of cell types to permit islets to be positioned at the interface of the 11% and 20.5% Ficoll layers. Islets are collected, washed and plated into culture plates until used.

EQUIVALENTS

This invention has been particularly shown and described with references to preferred embodiments thereof. It will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

CLAIMS

1. An artificial organ for implantation into a subject, comprising:

a first housing having at least one interior surface and at least one exterior surface, said at least one interior surface defining a chamber, at least a portion of said housing accessible to bodily fluids of said subject;

a membrane disposed within said chamber, at least a portion of said membrane selectively permeable to bodily fluids of said subject; and

one or more cells disposed within said selectively permeable membrane for producing a biological agent.

2. The artificial organ of claim 1, wherein said first housing includes a plurality of interconnected surfaces, two of said interconnected surfaces in closest facing relationship to each other being accessible to bodily fluids.

3. The artificial organ of claim 2, wherein said two interconnected surfaces are perforated so that bodily fluids pass transversely through said first housing and into said membrane.

4. The artificial organ of claim 2, wherein said

of selectively permeable membranes.

5. The artificial organ of claim 4, wherein said plurality of selectively permeable membranes is arranged in a pinwheel pattern.

6. The artificial organ of claims 2 or 4, wherein said membrane comprises a plurality of spaced-apart selectively permeable membranes arranged in parallel.

7. The artificial organ of claim 1, wherein said first housing and selectively permeable membrane define therebetween a volume that is accessible to bodily fluids.

8. The artificial organ of claim 1, wherein said selectively permeable membrane comprises a coiled tube.

9. The artificial organ of claim 1, further comprising a cellular growth factor disposed within said selectively permeable membrane.

10. The artificial organ of claim 1, wherein said cells comprise islet of Langerhans cells.

11. The artificial organ of claim 3, wherein said two surfaces include perforations with substantially circular cross-section.

12. The artificial organ of claim 3, wherein said two surfaces include a meshwork configuration.

13. An artificial organ for implantation into a subject comprising a first housing, having an interior surface and an exterior surface, said interior surface defining a chamber, said housing accessible to bodily fluids and in fluid communication with said exterior surface; a selectively permeable membrane disposed within said chamber, said membrane containing one or more cells capable of producing a biological agent; said one or more cells in in fluid communication with said chamber.

14. The artificial organ of claim 13, wherein said first housing is perforated to provide for flow of bodily fluids transversely through said chamber.

15. The artificial organ of claim 13, wherein said selectively permeable membrane has a length substantially greater than any linear dimension of said first housing.

16. The artificial organ of claim 13, further comprising a second housing disposed within said first housing, said second housing having an interior surface and an exterior surface, said interior surface of said first housing and said exterior surface of said second housing defining therebetween a volume, said selectively permeable membrane disposed within said volume.

17. The artificial organ of claim 16, wherein said second housing is accessible to bodily fluids.

18. The artificial organ of claim 17, wherein said selectively permeable membrane is supported on the exterior surface of said second housing.

19. The artificial organ of claim 18, wherein said selectively permeable membrane is disposed as a tube coiled around the exterior surface of said second housing.

20. The artificial organ of claim 13, wherein, said selectively permeable membrane is a coiled tube.

21. The artificial organ of claim 13, wherein said biological agent is a hormone.

22. The artificial organ of claim 13, wherein said selectively permeable membrane has a volume substantially equal to a volume of said chamber.

23. An implantable artificial organ comprising, a pair of concentrically arranged housings, a substantially annular volume defined between said concentrically arranged housing, at least one of said housings accessible to bodily fluids;

a selectively permeable membrane disposed within said annular volume;

cells disposed within said selectively permeable membrane for producing a biological agent.

24. The implantable artificial organ of claim 23, wherein each of said housings is a cylinder.

25. The implantable artificial organ of claim 24, wherein each cylinder of said pair of cylinders is perforated to provide for access to bodily fluids.

26. The implantable artificial organ of claim 25, wherein each cylinder of said pair of cylinders include ends that are perforated.

27. A method of delivering a beneficial agent to a subject, comprising the steps of:

implanting into a subject an artificial organ including:

a first housing, at least a portion of said housing accessible to bodily fluids of said subject; a membrane disposed within said first housing, at least a portion of said membrane selectively permeable to bodily fluids of said subject; and cells disposed within said membrane for producing a biological agent; and

allowing said biological agent made by said cell to be released into said bodily fluids of said subject.

28. The method of claim 27, further comprising monitoring said bodily fluids of said subject for production of said biological agent.

29. The method of claim 27, wherein the artificial organ is implanted into a body cavity of said subject.

30. The method of claim 29, wherein said body cavity comprises the pouch of Douglas.

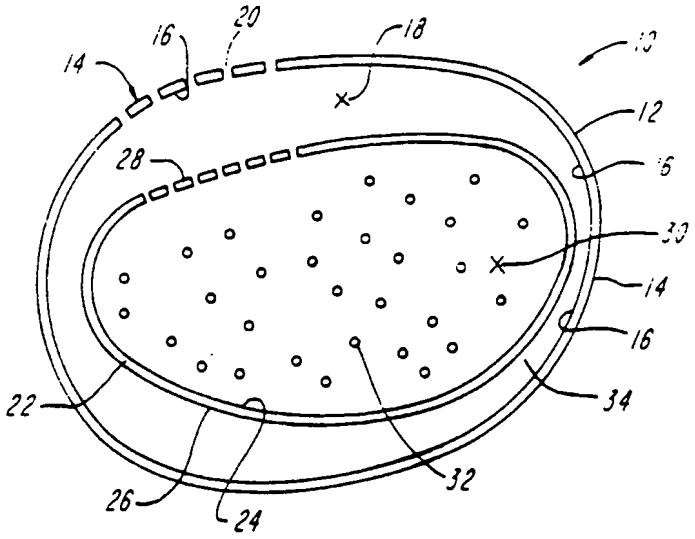

FIG. 1

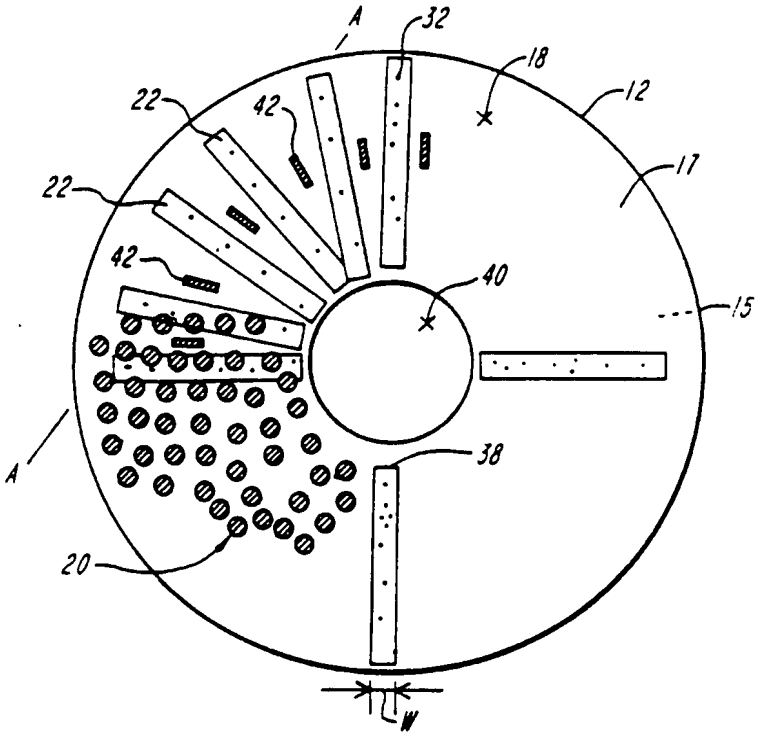

FIG. 2

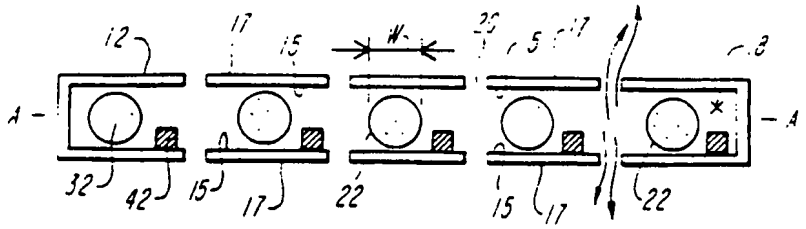

FIG. 3

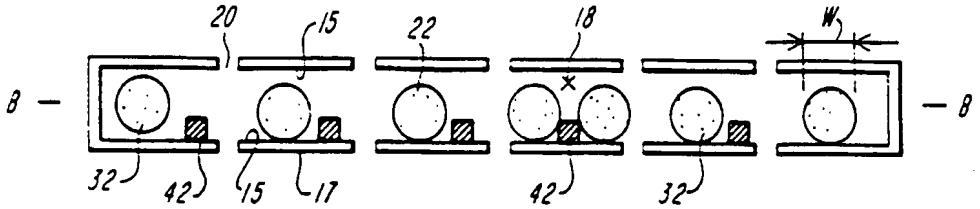

FIG. 5

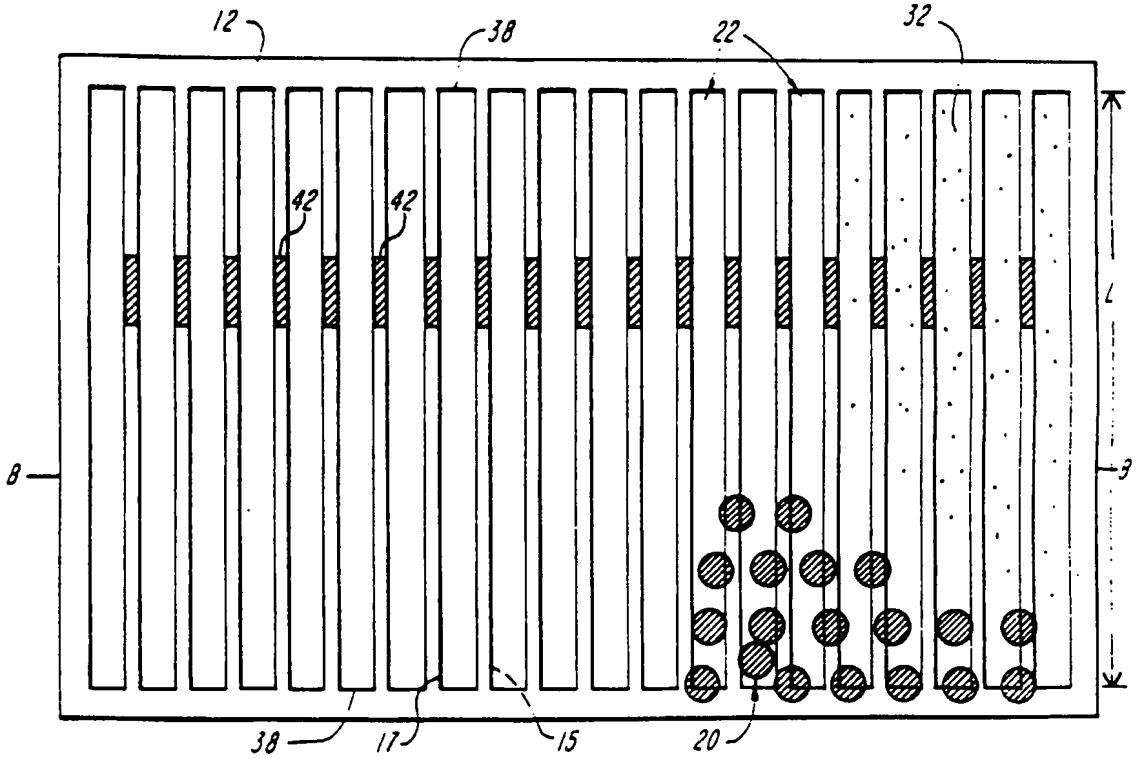

FIG. 4

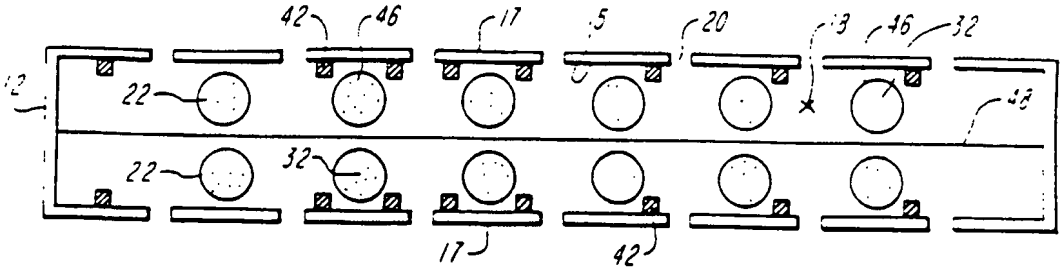

FIG. 6

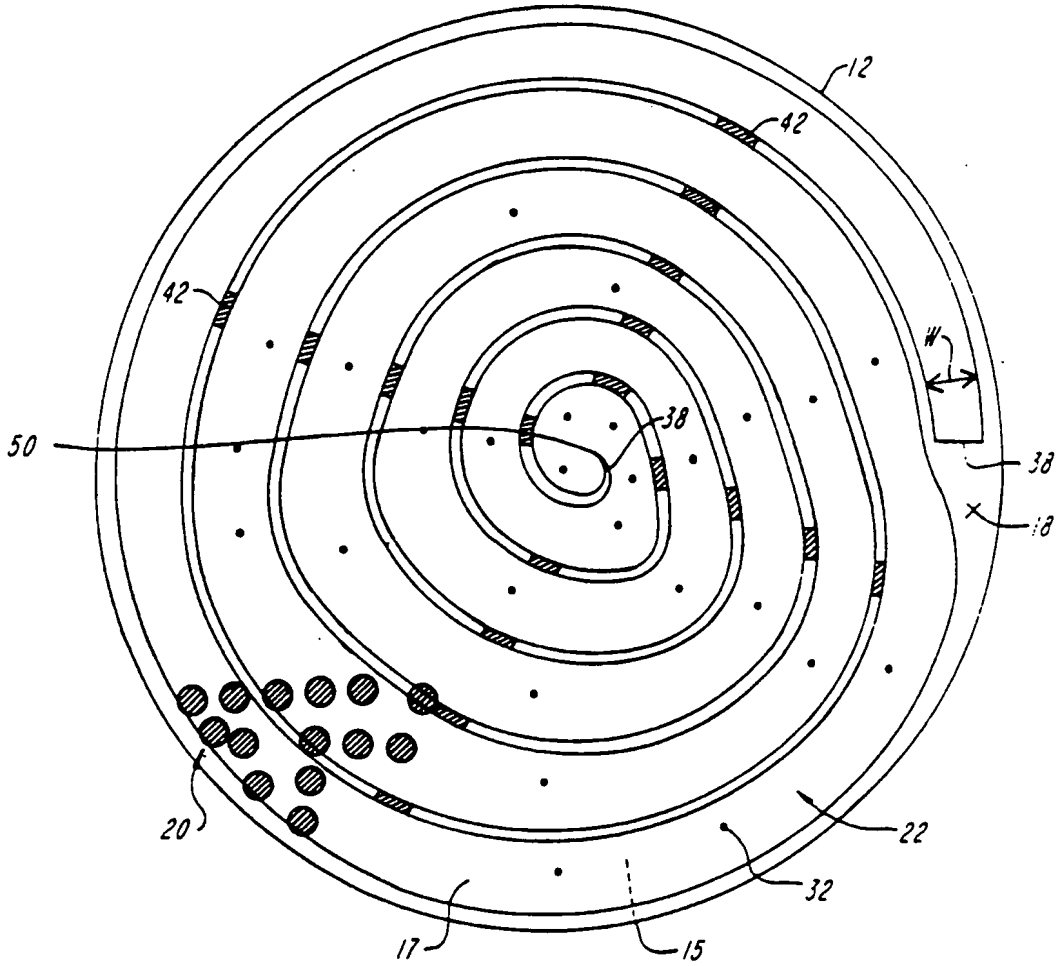

FIG. 7

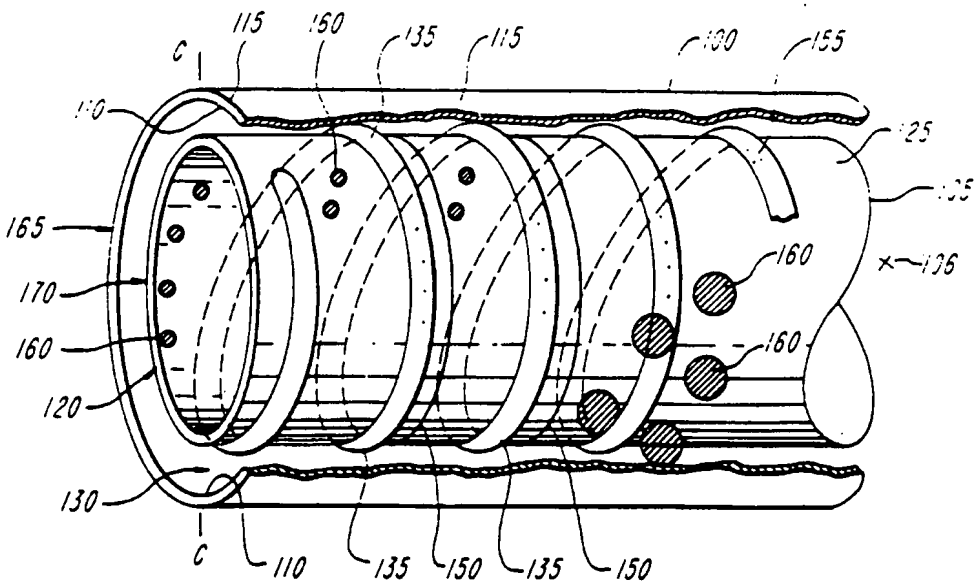

FIG. 8

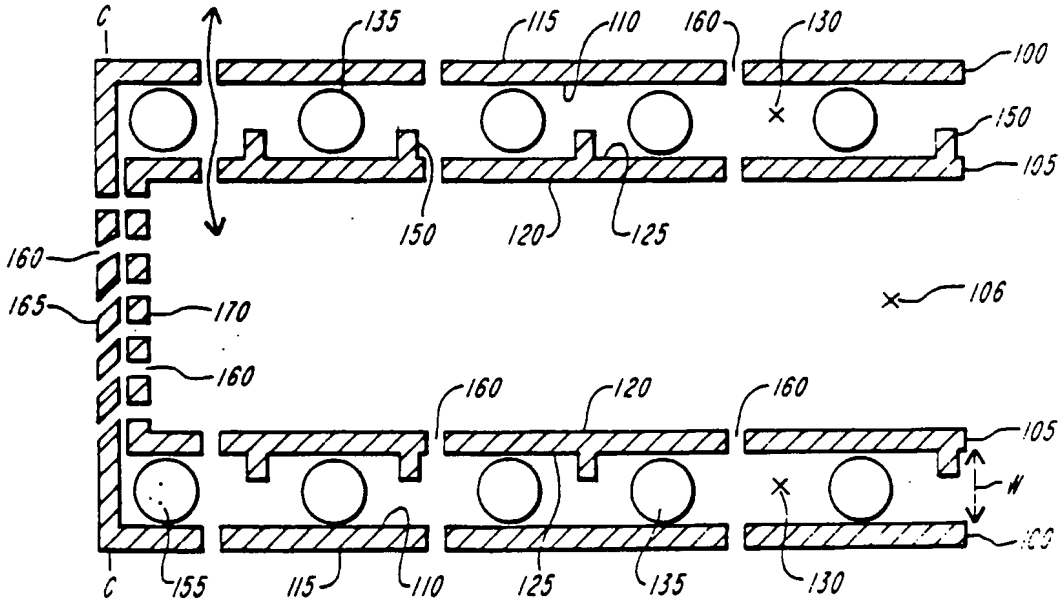

FIG. 9

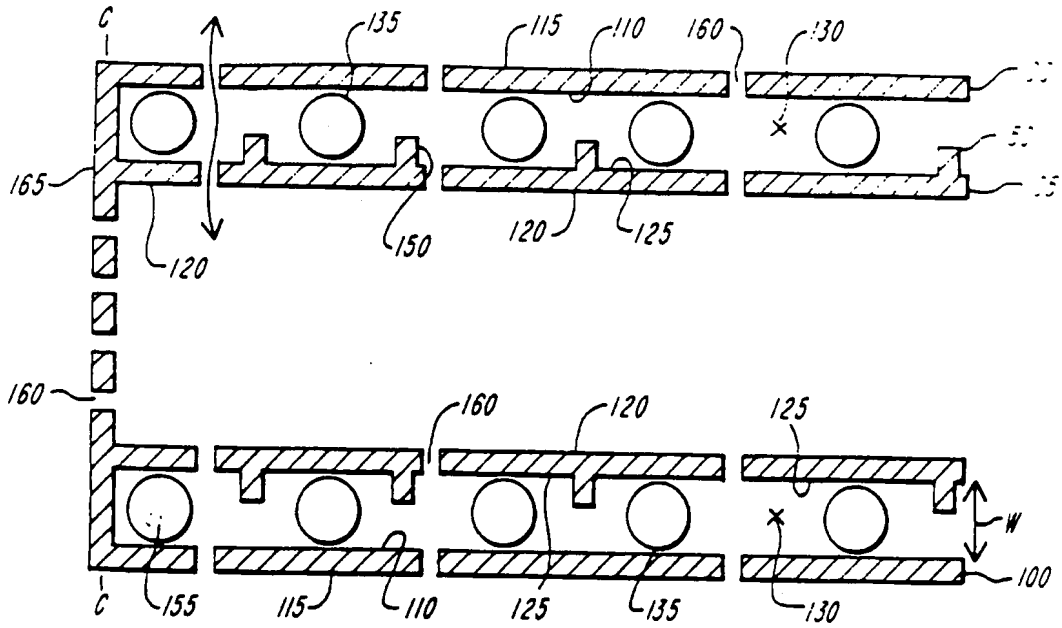

FIG. 10

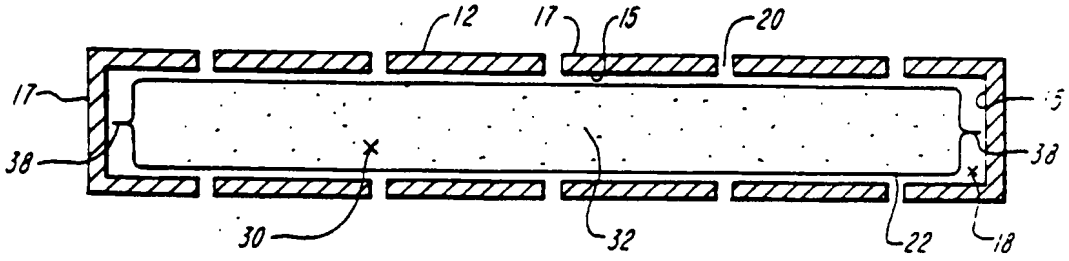

FIG. 11

INTERNATIONAL SEARCH REPORT

Inten. ..onal Application No
PCT/US 94/01734

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61F2/02 A61K9/00 C12N5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61F A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US,A,5 026 365 (ROSSINI ET AL.) 25 June 1991 see column 10, line 14 - column 11, line 50; figures	1,13,23 2-12, 14-22, 24-26
X	WO,A,91 00119 (BAXTER INTERNATIONAL INC.) 10 January 1991 see the whole document	1,13,23
X,P	WO,A,93 02635 (BAXTER INTERNATIONAL INC.) 18 February 1993 see page 6, line 7 - page 9, line 17; figure 1	1,13,23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
3 May 1994	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Sánchez y Sánchez, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter.. .onal Application No
PCT/US 94/01734

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB,A,1 479 002 (SPIELBERG) 6 July 1977 see the whole document	2-12, 14-22, 24-26
A	US,A,4 479 796 (KALLOK) 30 October 1984 see column 3, line 23 - line 42; figure 2	1-30
A	WO,A,87 03802 (SCHEREZENMEIR) 2 July 1987 see page 8, line 34 - page 9, line 20; figure 1	1
A	WO,A,93 00128 (BROWN UNIVERSITY) 7 January 1993 see the whole document	1
A	EP,A,0 188 309 (CONNAUGHT LABORATORIES LTD) 23 July 1986 see claims 1-7	1
A	EP,A,0 195 577 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 24 September 1986	

2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/01734

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 27-30
because they relate to subject matter not required to be searched by this Authority, namely:
Please see Rule 39.1(iv) PCT.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ..ional Application No
PCT/US 94/01734

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5026365	25-06-91	NONE		
WO-A-9100119	10-01-91	NONE		
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		CA-A-	2111978	07-01-93
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		JP-B-	5034946	25-05-93
		JP-A-	61209586	17-09-86
EP-A-0195577	24-09-86	CA-A-	1267851	17-04-90
		DE-A-	3685046	04-06-92
		FI-C-	90628	10-03-94
		JP-A-	61222443	02-10-86
		US-A-	4696286	29-09-87